The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 57

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JEAN P. PRIEELS,
NATHALIE M.C. GARCON-JOHNSON
MONCEF SLAOUI, and PIETRO PALA

Appeal No. 2004-2080
Application No. 08/909,879

HEARD: June 9, 2005

Before WILLIAM F. SMITH, MILLS, and GREEN, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 19-24, all the claims in the application. Claim 19, the only independent claim pending, is representative of the subject matter on appeal and reads as follows:

19. A vaccine composition comprising:

(a) Human Immunodeficiency Virus (HIV) antigen;
(b) QS21; and
(c) 3-De-O-acylated monophosphoryl lipid A (3D-MPL).

The evidence relied upon by the examiner is:

Fahey et al. (Fahey), "Status of Immune-Based Therapies in HIV Infection and AIDS," Clin. Exp. Immunol., Vol. 88, pp. 1-5 (1992)

Fox, "No Winners Against AIDS," Bio/Technology, Vol. 12, p. 128 (1994)

Haynes et al. (Haynes), "Update on the Issues of HIV Vaccine Development," Ann. Medicine, Vol. 28, pp. 39-41 (1996)

Cohen, "Jitters Jeopardize AIDS Vaccine Trails," Science, Vol. 262, pp. 980-981 (1993)

Butini et al. (Butini), Comparative Analysis of HIV-Specific CTL Activity in Lymphoid Tissue and Peripheral Blood," J. Cell. Biochem., Supplement 18B, Abstract No. J306 (1994)

Claims 19-24 stand rejected under 35 U.S.C. § 112, first paragraph (enablement). We reverse.

Background

The technology described in the specification relates to "vaccines containing QS21, an Hplc purified non-toxic fraction derived from the bark of Quillaja Saponaria Molina, and 3 De-O-acylated monophosphoryl lipid A (3 D-MPL). Id., page 1, lines 5-7. One of the parent applications to which this application claims priority under 35 U.S.C. § 120 issued as United States Patent 5,750,110 ('110 patent). Claim 1 of the '110 patent reads as follows:

1. A vaccine composition comprising:

   (a) an antigen;
   (b) QS21; and
   (c) 3-De-O-acylated monophosphoryl lipid A (3D-MPL).

As seen, appellants have already received patent protection for a vaccine composition which comprises an antigen broadly in combination with QS21 and 3D-MPL. On its face, claim 1 of the '110 patent includes the subject matter sought to be patented in this application. Indeed, in response to an obviousness-type double patenting rejection, appellants filed a Terminal Disclosure over the '110 patent. See Paper No. 43.

Despite the subject matter involved in this appeal being included within the scope of the claims of the '110 patent, the examiner has determined that claims 19-24 on appeal are non-enabled. The examiner states:

> It is well known in the art that retroviral infections in general, and HIV infections in particular, are refractory to anti-viral therapies. The obstacles to therapy of HIV are well documented in the literature. These obstacles include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus; 4) the ability of the virus to evade immune responses in the central nervous system due to the blood-brain barrier; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed invention with a reasonable expectation of success and without undue experimentation.

Examiner's Answer, paragraph bridging pages 4-5.

In response to the rejection, appellants rely upon two declarations filed by Dr. Gerald Voss executed April 6, 1998 and January 15, 1999 (Voss I and Voss II, respectively). Dr. Voss states in Voss I:

> 10. Currently, the best model to study anti-HIV vaccines is the simian-human immunodeficiency virus (SHIV) infection of the rhesus monkey. The chimeric SHIV expressing the HIV-1 Env protein allows for the evaluation of HIV-1 vaccines in a simple and relevant animal model. Infected animals mount a vigorous immune response similar to those observed in infected humans, including CD8+CTL. In contrast to the HIV-1 infection of chimpanzees, infection of rhesus monkeys with some SHIV strains induces typical AIDS-like symptoms. The most prominent feature of this disease induction is a rapid CD4+ cell decline. Molecular clones of the pathogenic virus have now been characterised.

Id., para. 10 (reference citations omitted). Dr. Voss goes on to state in his first declaration that a number of experiments have been carried out to investigate the combination of QS21 and 3D-MPL as vaccine adjuvants for the development of human anti-HIV vaccine and includes studies in murine and rhesus monkey models as well as phase I human trials. Id., para. 12. The phase I human trial is discussed by Dr. Voss as follows:

> 15. A phase I study, to investigate human application of an HIV vaccine, has been performed. Such trials are primarily designed for the purpose of measuring the safety, reactogenicity, and volunteer tolerance of the vaccine candidate. The phase I trial was successful in that it demonstrated the immunogenicity and safety of such an HIV vaccine. Work is now continuing in this area with the aim of future clinical studies.

Id., para. 15.

The rhesus monkey experiments are discussed by Dr. Voss as follows:

> 19. In the experimental studies performed, vaccination regimes comprising 3D-MPL and QS21, and the well known and characterised $gp120_{W6.1D}$ (recombinantly produced in CHO cells using a sequence derived from the HIV strain W6.1D) were successful in inducing strong in vitro virus neutralising humoral responses. The vaccination regime induced protection from challenge with the homologous $SHIV_{W6.1D}$ virus, in two of the four vaccinees. This homologous virus strain initiates a clinical infection which does not progress to AIDS-like symptoms, it is therefore a valid model for investigating vaccine prophylaxis of HIV infection. All of the control animals became infected (n=4). The formulations used and the results obtained are summarised in tables 4, 5 and 6.

Id., para. 19 (reference citation omitted).

Dr. Voss provides further information in his second declaration. First, Dr. Voss states:

> 7. In the Rhesus monkey SHIV model described in my previous declaration, the vaccines comprising QS21 and 3D-MPL adjuvants have been shown to induce protection in two out of four vaccinees. Thus, in the two monkeys that were protected there was no detectable viral burden or viral load. This protection from infection was observed despite the lack of interpretable CTL data.
>
> 8. Also, the monkeys that were infected (2 out of 4) did in fact show a reduced viral burden as evidenced by delayed HIV Polymerase Chain Reaction (PCR) and reduced virus isolation (Quantative Virus Isolation (QVI)) in comparison to negative control animals. These results were published recently in Mooij et al., 1998, AIDS, 12:F15-F22. A copy of this article is provided in Annex I.

Voss II, paras. 7 and 8. Dr. Voss concludes:

> 12. In conclusion, vaccines of the present invention, namely combinations of 3D-MPL and QS21, together with HIV antigen, have been

> shown to have efficacy in one of the best animal models currently available for the investigation of potential prophylactic HIV vaccines.

Id., para. 12.

The examiner's response to appellants' rebuttal is based upon the examiner's refusal to accept the SHIV monkey model as an appropriate animal model for HIV vaccines. As stated by the examiner:

> Appellants' affirmative evidence all relate[s] to the use of the SHIV/macaque animal model as a suitable animal model for AIDS. This is the arguments relating to the declarations of Voss and the references of Mooij and Joag referred to by Appellants. However, none of Appellants' evidence establishes a correlation between the results in the animal model and in vivo efficacy in humans. As set forth by the courts, such a correlation is required for the use of an animal model to support in vivo efficacy in humans. As stated during prosecution, the Court has indicated that 'inherent in the concept of the "standard experimental animal" is the ability of one skilled in the art to make the appropriate correlations between the results actually observed with the animal experiments and the probable results in human therapy.' In re Hartop, 135 USPQ 412 at 426 (CCPA 1962). At this point in time no such correlations have been made because no efficacy in humans has been shown that the animal model(s) could correlate with. Even Appellants' own rebuttal evidence bears out the Examiner's position. Joag concludes that 'While no individual model meets all the criteria for an ideal model, the available primate models collectively constitute a powerful tool to address almost any question in AIDS research' (see Appellant's [sic] Exhibit 8, page 227, paragraph bridging columns 1-2, last sentence). So even Joag, so heavily relied upon by Appellants, concludes that 1) no animal model meets all the criteria for an ideal animal model; 2) it takes all the primate models used collectively to provide a powerful tool for AIDS research; and 3) even using the collective animal models together, not all questions in AIDS research can be answered using the animal models. This is exactly the Examiner's point. Many researchers are using many different animal models for studying HIV. Many researchers have their own particularly favorite animal models. Yet, none of these animal models to date have

> been shown to effectively correlate with efficacy in humans. Therefore, it is the Examiner's position that Appellants' reliance on the data from a single animal model, the SHIV/macaque model, is insufficient to allow one skilled in the art to make and use the vaccines and method of the claimed invention with a reasonable expectation of success and without undue experimentation.

Examiner's Answer, paragraph bridging pages 10 and 11.

Discussion

Our appellate reviewing court has stated:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

Here, we do not find an argument by appellants that the examiner did not properly shift the burden to them to establish the enablement of the claimed invention.[1] In considering the respective positions of the examiner and appellants in regard to the rebuttal evidence, we find that appellants have the better argument.

[1] Nor is it seen that appellants could have reasonably made such an argument since it is readily apparent that the field of HIV vaccines is unpredictable. That factor alone can be sufficient to shift the burden to appellants to come forward with adequate proof that their claimed invention works as described. Marzocchi, 439 F.2d at 223, 169 USPQ 370.

We, like appellants, find the court's decision in In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995) instructive in resolving the issue presented in this appeal. The court made several observations in Brana that are relevant in considering the examiner's enablement rejection. First, the court cited In re Krimmel, 292 F.2d 948, 130 USPQ 215 (CCPA 1961) for its holding that it was the court's "firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made an significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans." Id., 292 F.2d at 953, 130 USPQ at 219. Furthermore, the court stated in Brana that "[u]sefulness in patent law and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Brana, 51 F.3d 1568, 34 USPQ2d at 1442.

Here, the examiner has not come to grips with the guidance provided by Brana. Despite appellants' reliance upon Brana in the Appeal Brief, the examiner does not cite to or discuss Brana in any manner. It may be that the vaccine of the present claims will in the end prove not to be useful in humans. However, as set forth in Brana, that does

not mean that the claims on appeal fail to comply with the enablement requirement of the first paragraph of § 112. Thus, the examiner's concern that human efficacy has not been demonstrated is misplaced.

As to the examiner's concerns that the SHIV/macaque is but one of many available primate models used by HIV researchers, we point out that appellants' evidence establishes that the model used by Dr. Voss is one of the accepted models used in this art area. Li[1] describes this model and its acceptance by researchers in this field in 1992, a date prior to the effective filing date of the claims on appeal. Li states:

> The experimental system described here (the infection of cynomolgus monkeys with the SHIV-4 virus) should provide a valuable model for study of the efficacy of anti-HIV-1 vaccines. The ability of such vaccines to induce protective immune responses in monkeys to infection by SHIV-4 should provide an indication of efficacy against viruses with HIV-1 envelope glycoproteins. The model can also be used to evaluate the ability of polyclonal and monoclonal antibodies to inhibit HIV-1 envelope function in animals. Therapeutics designed to inhibit the HIV-1 tat, rev, or env functions can also be evaluated in this model system.

Id., page 645, last paragraph. Thus, the model chosen by appellants is a "standard experimental animal" as discussed in Krimmel, supra.

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[1] Li, "Infection of Cynomolgus Monkeys with a Chimeric HIV-1/SIV_{mac} Virus That Expresses the HIV-1 Envelope Glycoprotines," Journal of Acquired Immune Deficiency Syndromes, Vol. 5, pp. 639-646 (1992) (Appeal Brief, Exhibit 4)

The decision of the examiner is reversed.

REVERSED

William F. Smith
Administrative Patent Judge

Demetra J. Mills
Administrative Patent Judge

Lora M. Green
Administrative Patent Judge

) BOARD OF PATENT
) APPEALS AND
) INTERFERENCES

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